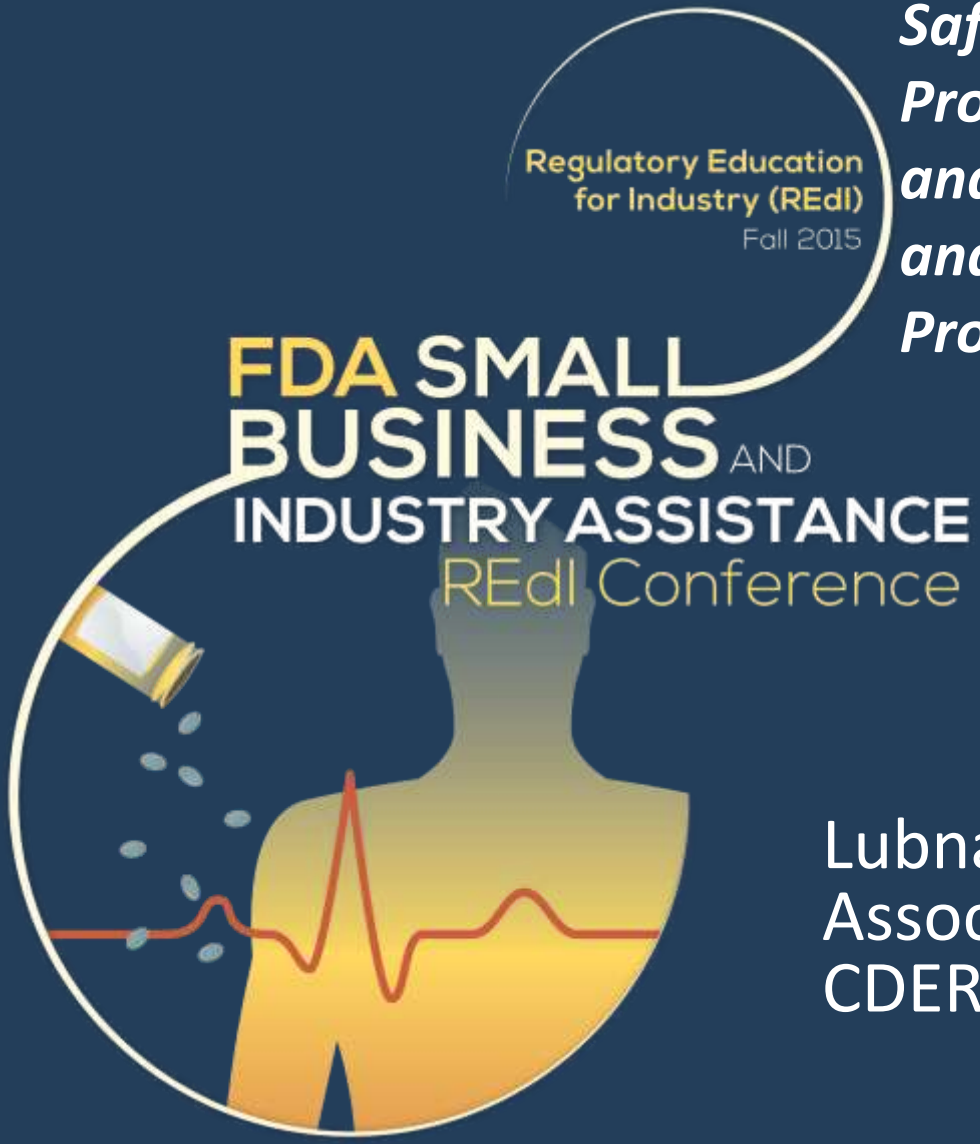
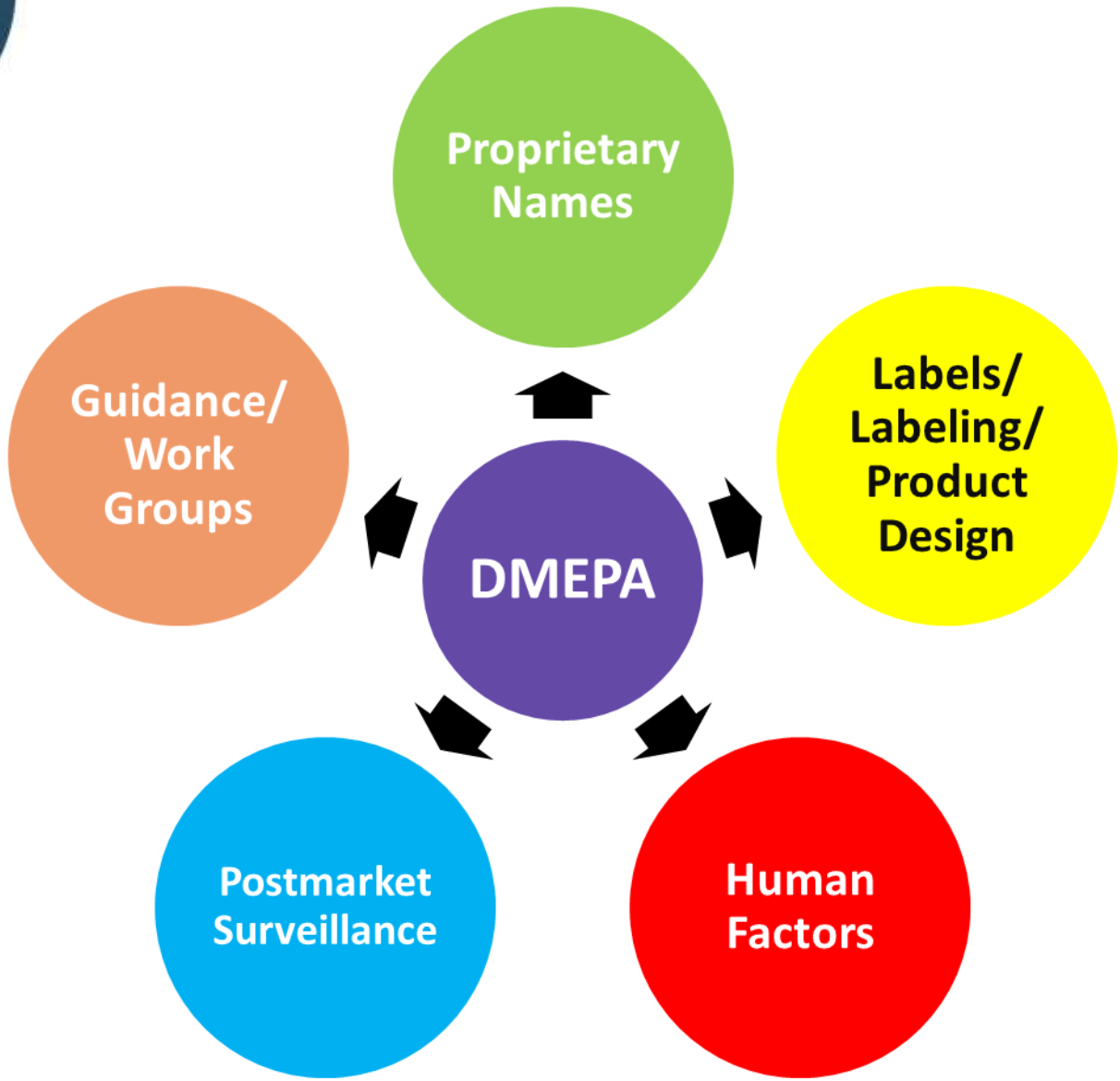


Safety Considerations for Product Design, Container Labels, and Carton Labeling and Best Practices in Developing Proprietary Names for Drugs

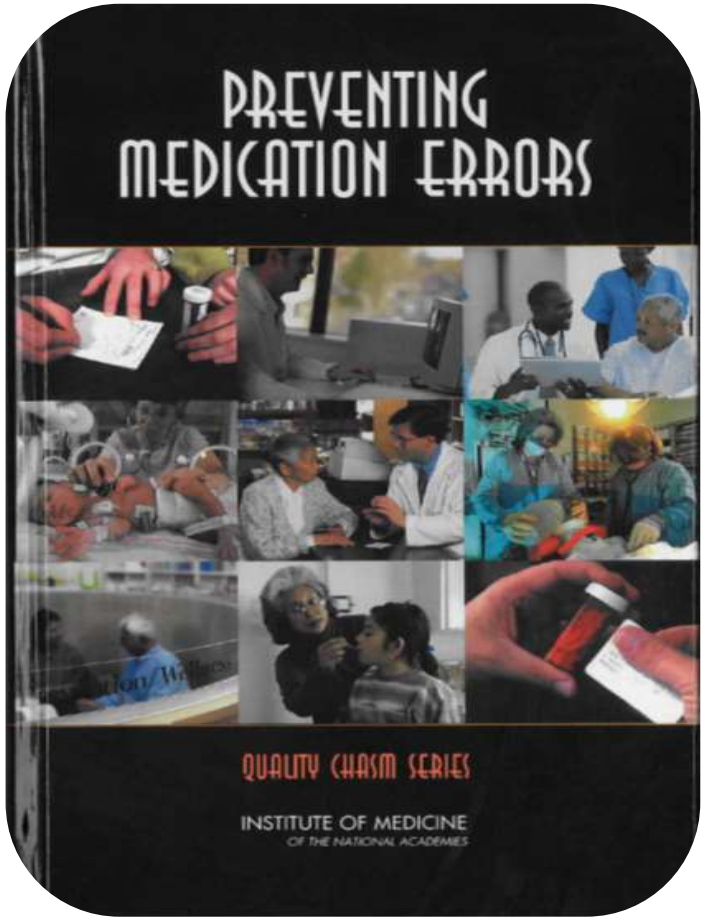
Lubna Merchant, M.S., PharmD
Associate Director, DMEPA
CDER/OSE/OMEPRM

Division of Medication Error Prevention and Analysis

Consultative → 1° Review/Signatory Authority for proprietary names


Proprietary Names
Labels/ Labeling/ Product Design
Human Factors
Postmarket Surveillance
Guidance/ Work Groups
DMEPA

2006 IOM Findings and Recommendations



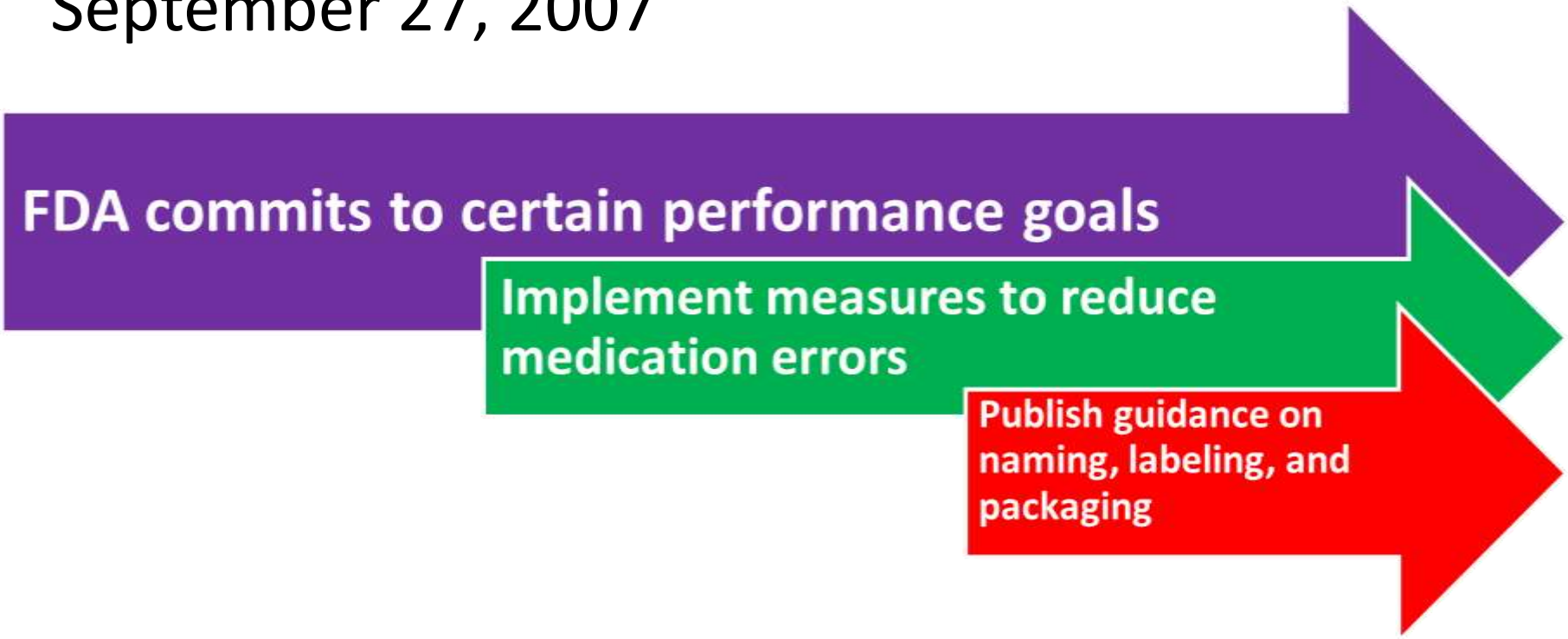
On average a hospital patient is subject to at least one medication error per day

Labeling and packaging issues cause of 33% of medication errors

Urged FDA to use Human Factors analysis to improve labeling information and nomenclature

PDUFA IV
Reauthorization and Expansion

Signed into law as part of FDAAA on September 27, 2007



FDA Guidance

- A “draft guidance,” when finalized, represents the FDA current thinking on a topic.
- Guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

Draft Guidance 1: ***Safety Considerations for Product Design to Minimize Medication Errors***	**Draft Guidance 2:** ***Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors***	**Draft Guidance 3:** ***Best Practices in Developing Proprietary Names to Minimize Medication Errors***	***Final Guidance Contents of a Complete Submission for the Evaluation of Proprietary Names***
Issued December 13, 2012, comment period closed February 2013	Issued April 24, 2013, comment period closed June 2013	Issued May 28, 2014, comment period closed September 2014	Issued February 2010
Provides sponsors with a set of principles for developing RX and OTC drug products using a systems approach to minimize medication errors relating to product design	Focuses on safety aspects of Rx container label and carton labeling design	Presents FDA's current thinking on best practices for developing and selecting proposed proprietary names	This guidance describes the information that FDA uses to evaluate proposed proprietary names for certain drugs, including biological products.

Guidance for Industry

Safety Considerations for Product Design to Minimize Medication Errors

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

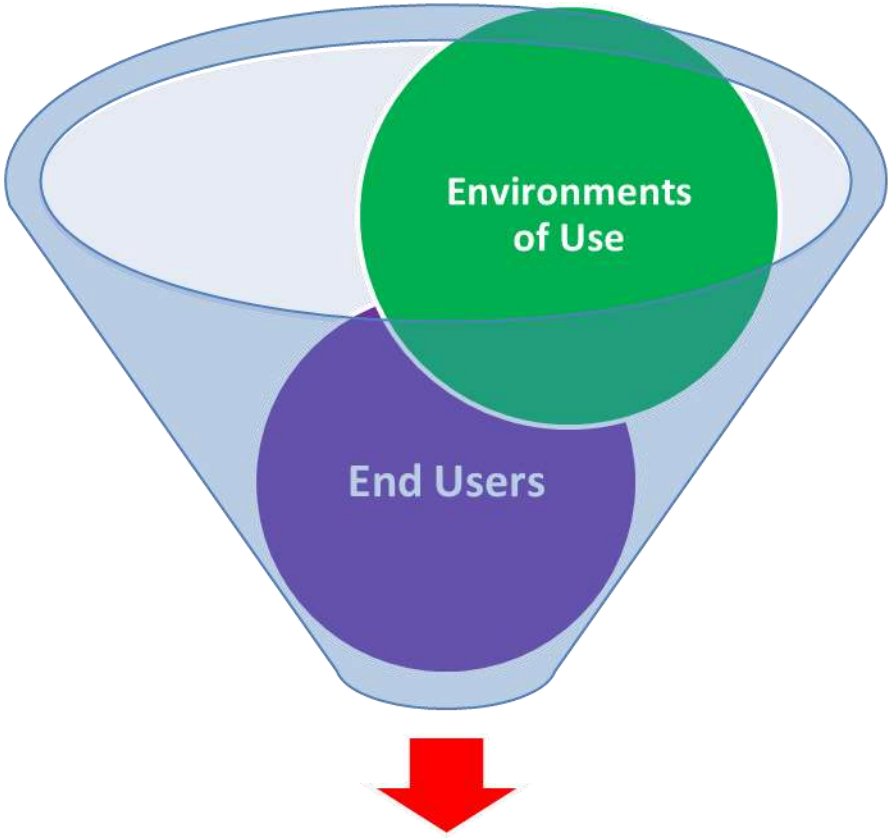
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov/ Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER), Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Carol Holquist at 301-796-0171.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2012
Drug Safety

Early Stage Considerations

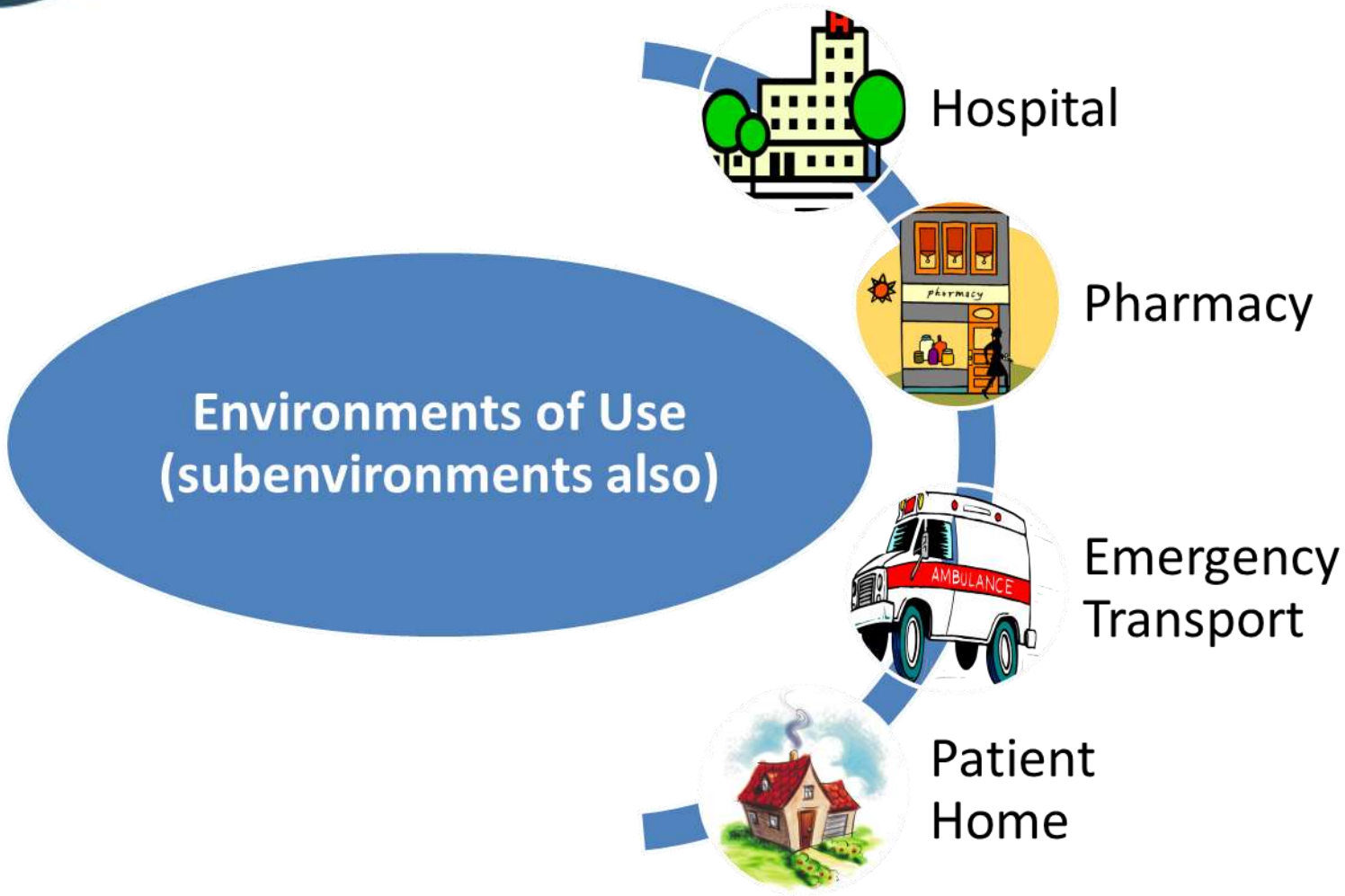


Identify risks that can lead to medication error

End Users: Questions to Ask

- Who are the end users?
- Are there multiple user groups?
- How diverse are the end users?
- What critical tasks must the end user perform?
- Is extensive manipulation or cognitive process required to use the product?
- Are there physical or mental limitations?

Early Stage Considerations



Environments of Use: Questions to Ask

- In what environment will product be used?
- What environmental factors need to be considered?
- How are drugs stored and obtained in the environment?
- Are there similar products used in the environment?
- Is the product a variant of something already used in this environment?

Drug Product User Interface

- Evaluate how and why problems have occurred with similar products
  - Identify error prone features and eliminate them from design
  - Prevent same errors from occurring
- Sponsors should consider lessons learned to minimize risks associated with their designs

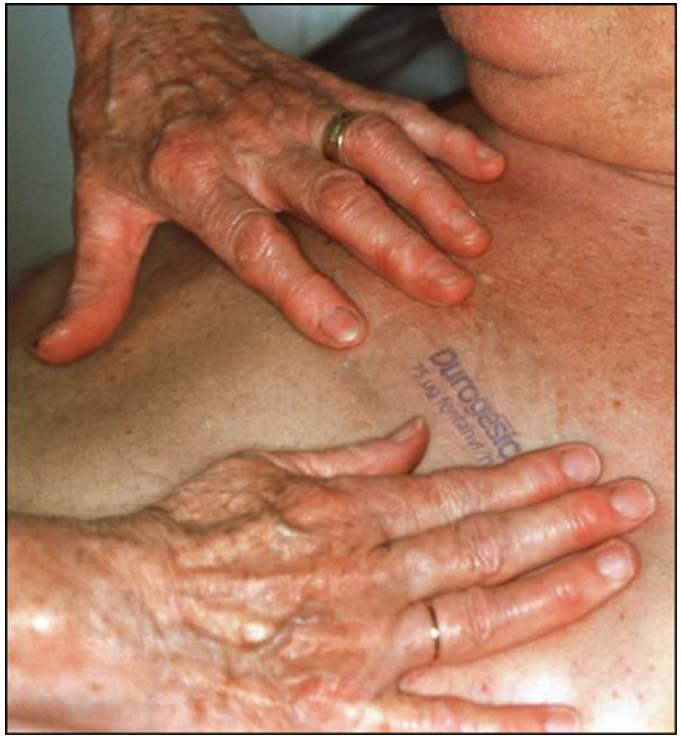
Examples of Known Problems Due to Product Design

- Solid Oral Dosage Forms
  - Product resembles candy
  - Choking hazard
    - Sticky coating
    - Large size
    - Larger cross sectional area
    - Propensity for swelling
  - Too hard/Too friable

Examples of Known Problems Due to Product Design

- Product Line Extensions
  - Creating extended-release product strength(s) that overlap in strength(s) with immediate release products
  - Creating extended-release product strengths that are achievable from the marketed immediate-release product strength(s)

Special Considerations for Transdermal Products



- Include an identifying label on the backing membrane that includes the Drug Name and Strength.
- Transdermal system strength should be presented as a transdermal delivery rate (e.g. XX mg/day).
- Ensure the ink has adequate contrast (i.e. is visible) for the duration of patch wear
- Clear patch difficult to see on skin

Examples of Known Problems Due to Product Design

- Inconsistency between drug product strength and dosing
  - Multiple units (e.g. tablets, capsules, vials, syringes) required to achieve a usual single dose
    - Dosing errors due to miscalculations
    - Dosing errors due to forgetting how much has already been administered

Examples of Known Problems Due to Product Design

A Dosing directions from packaging

Age (yr)	Starting Dose	Maximum Dose
Under 2	Consult Physician	Consult Physician
2 to under 6	0.5mL to 0.75mL Once a day	0.75mL Twice a day
6 to under 12	1mL to 1.5mL Once a day	1.5mL Twice a day

Missing marking
(absent from measuring device)

Superfluous marking
(not listed in dosing directions)

B Measuring device

Dosing cup measures CC, mL, TBSP, Tsp, drams and fluid ounces

- Dosing Devices not appropriate for dosages to be measured
- Difficult to see dose markings on dosing device
- Multiple units of measures on a dosing device

Examples of Known Problems Due to Product Design

- Intravenous Products
  - 2 step dilution for a product already in solution
    - Overdoses due to failure to dilute product
    - Improper doses due to incorrect dilution
  - Co-packaging of special diluent
    - Diluent separated from dry powder
    - Confusing diluent as drug

Reported Problems with Container Closure Design

- Container closures that look similar within a product line
- Container closures serving as labels that have illegible information

Reported Problems with Container Closure Design

Capsules for inhalation swallowed whole

Reported Problems with Container Closure Design

Topical products packaged in container/ closures that look similar to eye, ear, nasal, or oral products

Reported Problems with Container Closure Design

Drug-device combinations with complex controls or unexpected device operation

Proactive Risk Assessments

- Develop drug products using analytical methods to investigate, understand, and correct identified risks
- These methods should be applied early in drug development to build safety into the product design and throughout a drug product's life cycle
- Failure Mode and Effects Analysis
  - Systemic evaluation of proposed product within the medication use system
  - Provides understanding of relative impact of different types of system failures
  - Considers everyone in the medication use process

Proactive Risk Assessments

- CDER recommends human factors studies be conducted to characterize risks as well as develop mitigation strategies.

- Simulated Use Testing
  - Systematic collection of data from representative participants in realistic situations
  - Help determine whether users can safely and correctly perform critical tasks
  - Seeks to assess actual use
  - Results can be used to update the FMEA

Guidance for Industry

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

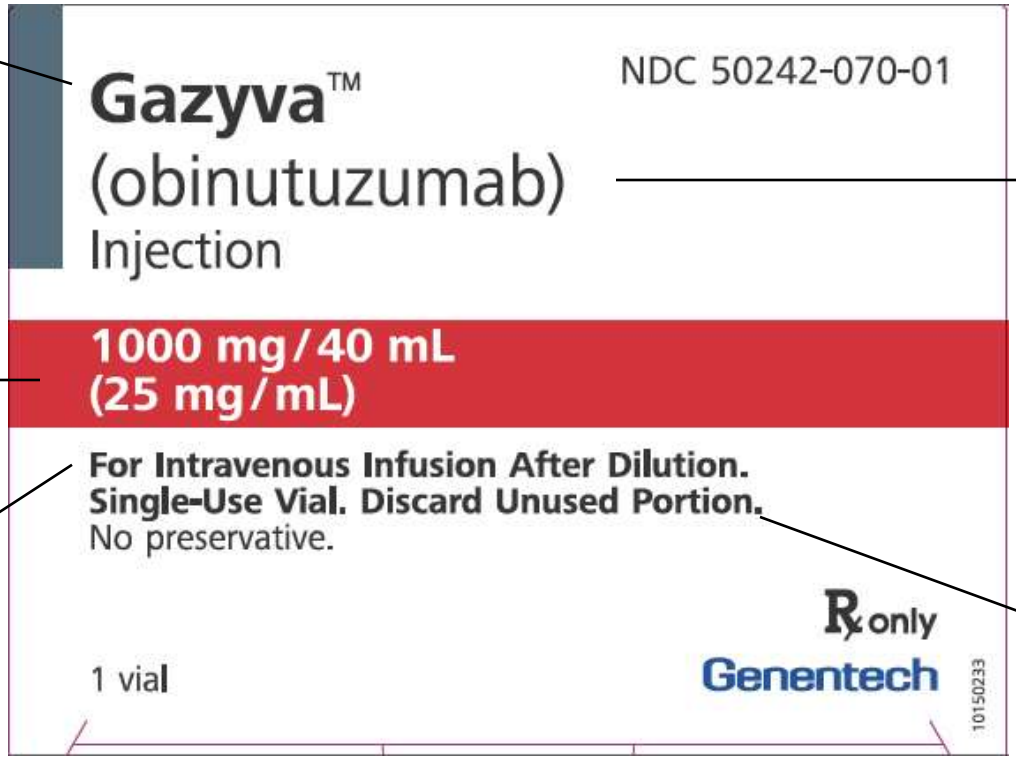
April 2013
Drug Safety

General Considerations

- Considering end users and environments of use during drug development can allow identification of risks that can lead to error
- Sponsors should assess and minimize the risk for medication errors due to labels and labeling
- Refer to analytical methods for risk assessments outlined in draft Guidance-Safety Considerations for Product Design to Minimize Medication Errors

Principal Display Panel (PDP)

Proprietary Name



Established Name or Proper Name

Product Strength

Route of Administration

Warning/ Cautionary Statements

Container Label Size: General Considerations

- Exemptions from some drug labeling requirements can be made under 21 CFR 201.10(i)
  - Proprietary name and established name (if any)
  - Product strength
  - Lot number
  - Name of manufacturer, packer, or distributor
- USP requires labels of official drug product to bear an expiration date

Container Label Size: General Considerations

- Biologic Products
  - Minimum requirements under 21 CFR 610.60(c)
    - Name of product
    - Lot number
    - Manufacturer name
    - Recommended individual dose for multiple dose containers

Text Size and Style: General Considerations

- Choose easy to read font, not lightweight or condensed
  - Improved readability with larger font size such as 12-point sans serif (e.g. Arial)
- 12-point font preferred when label size permits

Contrast of Text and Background: General Considerations

- Choose text and background color to afford adequate legibility of text
- Avoid color combinations that do not afford maximum legibility of text

Proprietary Name

Established Name

Information Crowding/Visual Clutter: General Considerations

- Crowded labels may make important information difficult to read or easily overlooked
- Separate lines or blocks of text with sufficient white space
- Move less important information to back panels, side panels, or prescribing information
- Remove information about business partnerships (apart from required manufacturer, distributor, or packer information)

Information Crowding/Visual Clutter: General Considerations

- Discourage use of:
  - Logos
  - Bars
  - Stripes
  - Watermark graphics
  - Lines
  - Symbols

Images of Tablets/Capsules: General Considerations

- Can help healthcare professionals confirm they are dispensing the correct medication
- Images should appear at bottom of labels and labeling
- Should not compete in size or prominence with proprietary name, established name, or strength
- Images should represent the actual tablet or capsule, reflecting true size, color, shape, and imprint.
- Do not recommend use of schematic or computer-generated images

Dangerous Abbreviations, Acronyms, and Symbols: General Considerations

- Certain abbreviations, acronyms, and symbols are dangerous and should not be used
  - Misinterpretations can lead to mistakes
- Non-standardized abbreviations, symbols, and dose designations can also lead to mistakes
- Refer to The Joint Commission's "Do Not Use" list
- Refer to the Institute for Safe Medication Practices (ISMP) "List of Error Prone Abbreviations, Symbols, and Dose Designations"

Typical Pharmacy Shelf

Look-alike Container Labels and Carton Labeling: General Considerations

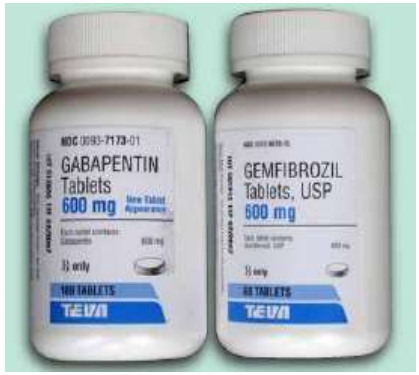
- Encourage Sponsors to create labels and labeling sufficiently distinct from that of their other products and the products of other manufacturers
- Consider when products are customarily stored side-by-side or near one another

Examples of Look-Alike Trade Dress

Adderall XR

Citalopram

Clonazepam (Teva)



Teva

Pfizer

Color Coding: General Considerations

- Use color to designate a specific meaning
- FDA generally recommends avoiding color coding in most instances
  - Reserved for special circumstances after human factors testing and feedback on the prototype from all end users is received and evaluated by FDA prior to use

Color Coding: General Considerations

- Certain applications of color coding are appropriate (e.g. warfarin)

COUMADIN® (warfarin sodium)

1 mg	2 mg	2.5 mg	3 mg	4 mg	5 mg	6 mg	7.5 mg	10 mg
								

Color Coding: General Considerations

- Color coding can sometimes lead to confusion

Special Considerations for Proprietary, Established, and Proper Names

- 21 CFR 201.10(g)(2) and 21 CFR 610.62
- Established name for **drug products** should include finished dosage form
- Proper name for **biological products** should not include finished dosage form

Drug Product:

Mydrug (drugozide injection)	Mydrug (drugozide) injection	Mydrug (drugozide) Injection

Biological Product:

Mydrug (drugozide) Injection	drugozide Mydrug Injection

Special Considerations for Product Strength

- Strength Differentiation: Make sure product strength stands out on the container label and carton labeling. Techniques include:
  - Boxing
  - Prominent typeface or type weight
  - Color differentiation

Special Considerations for Product Strength

- Strength Designations should use a consistent unit of measure across all elements of labels and labeling

Dosing for Perioperative Hypotension

Intravenous bolus administration: 50 mcg to 250 mcg

Special Considerations for Product Strength

- Small Volume Parenteral Products
  - USP General Chapter <1> *Injection*
    - Total quantity per total volume followed by concentration per milliliter (mL)

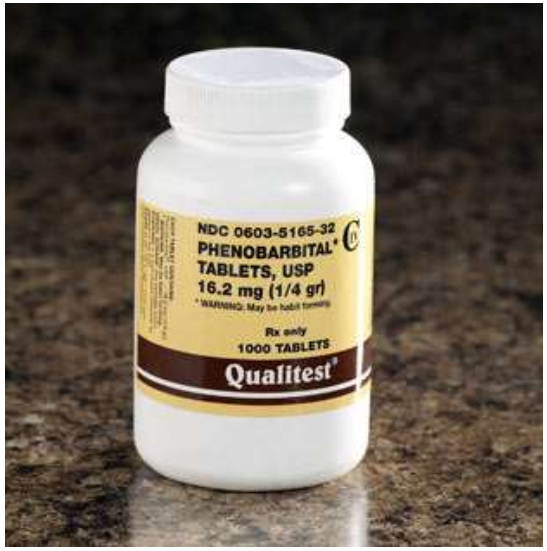
How many USP units are in this vial?

30,000 units

Special Considerations for Product Strength

- Metric Measurements
  - Dose or strength expression should appear in metric units of measure such as mL, mg, and mcg

1/4 gr?



Special Considerations for Route of Administration and Warnings for Critical Information

- Avoid use of abbreviations
- Use positive statements instead of negative statements
  - Easy to overlook the word “not”

    “Not for intrathecal use”
  - Affirmative statements help to ensure readers understand the intended route of administration, even if they do not read every word

    “For Intravenous Use only”

Guidance for Industry

Best Practices in Developing Proprietary Names for Drugs

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Kellie Taylor at 301-796-0157, or (CBER) Office of Communications, Outreach and Development at 800-835-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2014
Drug Safety

Draft Guidance for Industry: Best Practices for Developing Proprietary Names for Drugs

- Issued May 28, 2014
  - Comment period closed in September
- Joint Guidance with CDER and CBER
- Applies to Rx and OTC products
- Intended to help sponsors of drugs and biological products develop proprietary names that do not cause or contribute to medication errors or the misbranding of the drug
- Focus in drafting the guidance was to communicate a systematic, standardized, and transparent approach to proprietary name evaluation

Contents of Best Practices for Developing Proprietary Names for Drugs

I. Prescreening considerations for proprietary name candidates

II. Consider attributes that may be misleading or error-prone

III. Misbranding review
- Avoid names that overstate efficacy, minimize risks, or make unsupported suggestions of unique effectiveness or composition

IV. Methods for Evaluating Safety of Proposed Proprietary Names
- Avoid names with orthographic, spelling, and phonetic similarity to other names that could result in errors

Resources

- *Draft Guidance: Best Practices in Developing Proprietary Names for Drugs*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf

  Docket comments: http://www.regulations.gov/#!documentDetail;D=FDA-2014-D-0622-0001

- *CDER Small business and Industry Assistance Webinar on "Overview of FDA's Proprietary Name Reserve Process" July 15, 2014*

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm403376.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Guidance for Industry

Contents of a Complete Submission for the Evaluation of Proprietary Names

Additional copies are available from:
Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 51, Room 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or

Office of Communication, Outreach and
Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Drug Evaluation and Research (CBER)

February 2010
Labeling

Final Guidance

- Issued on February 5, 2010
- Clarified
  - PDUFA IV review performance timeframes
  - Clarified the purpose of guidance
  - Referenced the concept paper to provide a complete overview of the tools and methods used for FDA's safety evaluation that are mentioned in the proprietary names submission guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072229.pdf
- Complete Submission Guidance Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformati\on/Guidances/ucm075068.pdf

Introduction

- Guidance applies to proprietary name submissions for:
  - IND
  - NDA
  - BLA
  - ANDA
- Nonprescription drug products that are the subject of an NDA or ANDA.

How to Identify Proprietary Name Requests

- Initial requests, "**REQUEST FOR PROPRIETARY NAME REVIEW"** in bold, capital letters on first page of the submission.

- For amendments, **"AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW"** in bold, capital letters on first page of the submission.

- For reconsiderations, **"REQUEST FOR RECONSIDERATION OF PROPRIETARY NAME"** in bold, capital letters on first page of the submission.

IND Form 1571 & NDA/BLA/ANDA Form 356h

- Include reason for submission

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER _____

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION _____

Complete Submission Requirements

- Proposed Proprietary Name
  - Primary & Alternate
- Intended Pronunciation of the Proposed Proprietary Name(s)
- Derivation of Proprietary Name
- Intended Meaning of Proprietary Name Modifiers (e.g., prefix, suffix)
- Pharmacologic/Therapeutic Category
- Likely Care Environment for Dispensing & Use
- Delivery System (if applicable)
- Measuring Device (if applicable)

Complete Submission Requirements

- Established Name
- Prescription Status
- Dosage Form(s)
- Product Strength(s)
- Proposed Indication(s) for Use
- Route(s) of Administration
- Usual Dosage, Frequency of Administration, Dosing Interval, Maximum Daily Dose
- Dosing in Specific Populations
- Instructions for Use
- Storage Requirement
- How Supplied and Packaging Configuration

Independent Assessments

- FDA does not consider a submission incomplete because this information is not provided.
  - Encourage submission if conducted

- Does not substitute for requirements necessary for a complete submission

Review Clock

- Review clock will not begin if submission incomplete
- Review timelines for complete submissions
  - IND – 180 days
  - NDA – 90 days
  - BLA – 90 days
  - ANDA – No goal date for reviews

Paper or Electronic Submissions Accepted

- Need three copies for paper submissions
- Electronic submissions placed in eCTD section "1.12.4 Other Correspondence — Request for comments and advice."
  - The eCTD leaf title of the document should be clear, concise, and indicative of the document's content (e.g., "**REQUEST FOR PROPRIETARY NAME REVIEW**," "**AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW**," or "**REQUEST FOR RECONSIDERATION OF PROPRIETARY NAME**").
  - Provide the eCTD location of the contents on the first page of the submission and, if possible, include cross-document links or external bookmarks to the information. This approach will help ensure the information can be accessed quickly and easily.

Common Problems with Submissions

- Request not submitted to a pending application
- Request for name review for an approved product not submitted as a prior approval labeling supplement
- Paper submission not submitted in triplicate
- Only external assessment submitted
- The statement "**REQUEST FOR PROPRIETARY NAME REVIEW"** not included in bold, capital letters on the cover letter page of the submission.
- Names are not identified (primary versus alternate)
- Dosing and administration information incomplete

Contact: lubna.merchant@fda.hhs.gov

Please complete the session survey:

surveymonkey.com/r/DRG-D1S1